



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US99/24347 (22) International Filing Date: 19 October 1999 (19.10.99) (30) Priority Data: 09/178,347 23 October 1998 (23.10.98) US 09/354,017 15 July 1999 (15.07.99) US (71) Applicant: ABBOTT LABORATORIES [US/US]; Dept. 377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US). (72) Inventors: MAY, Thomas; 520 Merrill Lane, Grayslake, IL 60030 (US). HOFSTETTER, John; 1001 Stockton Court, Vernon Hills, IL 60061 (US). OLSON, Kathleen, L.; 1441 West Warner Avenue, Chicago, IL 60631 (US). MENON, Sukumaran, K.; 18045 Pond Ridge Circle, Gurnee, IL 60031 (US). MIKRUT, Bernard, A.; 275 Hickory Court, Lake Bluff, IL 60044 (US). OVENSHERE, Clyton, S.; 1016 Glenlake Avenue, Park Ridge, IL 60068 (US). RHODES, Lawrence, John; 448 North Crooked Lake Lane, Linden- hurst, IL 60046 (US). SPEICHER, Earl, R.; 510 Springside Lane, Buffalo Grove, IL 60089 (US). WATERSON, James, R.; 587 Edington Lane, Gurnee, IL 60031 (US).		(74) Agents: STEELE, Gregory, W. et al.; Abbott Laboratories, Dept. 377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US). (81) Designated States: AU, CA, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>
(54) Title: PROPOFOL COMPOSITION (57) Abstract The present invention is directed to a sterile pharmaceutical composition comprising a propofol containing oil-in-water emulsion formulation having as an antimicrobial agent, a member selected from the group consisting of benzyl alcohol and sodium ethylene diamine tetraacetate; benzethonium chloride; and benzyl alcohol and sodium benzoate.		

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Propofol Composition

5 Field of the Invention

The present Invention relates to pharmaceutical compositions containing 2,6-diisopropylphenol.

Background of the Invention

10 Propofol (2,6-diisopropylphenol) is an injectable anesthetic which has hypnotic properties and can be used to induce and maintain general anesthesia and sedation. Injectable anesthetics such as propofol are administered directly into the bloodstream. This results in a rapid onset of anesthesia influenced almost entirely by the rate at which the anesthetic agent crosses the blood-brain barrier. Therefore, the anesthetic agent must have
15 sufficient lipid solubility to be able to cross this barrier and depress the relevant mechanisms of the brain. Propofol is poorly water soluble and therefore is generally formulated as an emulsion. However, propofol containing emulsions have been shown to support microbial growth. Therefore it is desirable to formulate propofol emulsions in a manner in which microbial growth is prevented. Disodium EDTA (ethylenediamine
20 tetraacetate) has been shown to delay, but not prevent, the onset of microbial growth in propofol emulsions. See U.S. Patent No. 5,714,520.

Accordingly it is an object of the present invention to provide a propofol containing pharmaceutical composition that provides antimicrobial benefits above that found in existing compositions and/or prevents the onset of microbial growth in such compositions.

25

Summary of the Invention

The present invention is directed to a sterile pharmaceutical composition comprising a propofol containing oil-in-water emulsion formulation having as an antimicrobial agent, a member selected from the group consisting of benzyl alcohol; benzyl
30 alcohol and disodium ethylenediamine tetraacetate; benzethonium chloride; and benzyl alcohol and sodium benzoate.

Detailed Description of the Invention

The term "antimicrobial" means an agent which delays onset or retards rate of growth to less than 1 logarithmic increase over a 24 hour period as compared to an unpreserved formulation.

5 The composition of the present invention comprises an oil-in-water emulsion in which the 2,6-diisopropylphenol, either alone or dissolved in a water immiscible solvent, for example a vegetable oil, is emulsified with water by means of surfactant.

Typically the solvent is an oil such as soybean oil, safflower oil, cottonseed oil, corn oil, sunflower oil, arachis oil, castor oil, or olive oil. Preferably the oil is soybean oil.
10 Alternatively the solvent can be an ester of a medium or long chain fatty acid, for example a mono-, di-, or triglyceride; or a compound such as ethyl oleate, isopropyl myristate, isopropyl palmitate, a glycerol ester or a polyoxyl hydrogenated castor oil. Other suitable solvents may be marine oils, for example cod liver or other fish derived oils, or fractionated oils, such as fractionated coconut oil or modified soybean oil. The
15 composition of present invention may also comprise a mixture of two or more of the above water immiscible solvents.

The 2,6-diisopropylphenol, either alone or dissolved in the water immiscible solvent, is emulsified in an aqueous medium with the aid of a surfactant. Suitable surfactants include synthetic non-ionic surfactants, for example ethoxylated ethers and
20 ethoxylated esters, polypropylene polyethylene block copolymers, and phosphatides, as for example egg and soy phosphatides. Preferably, the surfactant is egg phosphatide.

Preferred compositions of the present invention comprise from 0.1 to 5.0% by weight, preferably 1 to 2% by weight, and most preferably 1% by weight of 2,6-diisopropylphenol; from 1 to 30% by weight, preferably 10 to 20% by weight of a water
25 immiscible solvent; and from about 0.2 to 2.0% by weight, preferably 1.2% by weight of a surfactant. The compositions of the present invention can also contain pH adjusting agents such as sodium hydroxide or hydrochloric acid so they can be formulated at a physiologically neutral pH.

The compositions of the present invention may also be made isotonic by the
30 incorporation of a suitable additive such as glycerol.

The balance of the composition is made up with water.

The antimicrobial systems utilized in the compositions of the present invention are selected from the group consisting of benzyl alcohol; benzyl alcohol and disodium ethylenediamine tetraacetate; benzethonium chloride; and benzyl alcohol and sodium benzoate. The concentration of the antimicrobial agents in the final composition will vary depending on the particular agent or agents selected. For instance in a preferred composition of the invention the amount of benzyl alcohol is in the range of about 0.0175% to 0.9% (w/v), more preferably about 0.07% to about 0.45%, most preferred in the range of 0.15%. In an alternate preferred composition of the invention, the amount of benzyl alcohol is about 0.07% to about 0.9%, optionally including an amount of disodium EDTA of about 0.005%. Yet another embodiment provides a composition including an amount of benzethonium chloride of about 0.01% to about 0.1%. Optionally, the composition of the present invention includes 0.07% sodium benzoate. The most preferred compositions of the present invention include benzyl alcohol and sodium benzoate. The compositions of the present invention may be prepared by conventional processes as for example that disclosed in U.S. Patent No. 5,714,520.

A particularly preferred composition of the present invention is as set forth below.

TABLE 1 (weight percent)

Component	Broad Range	Preferred Range	Particularly Preferred Amount
2,6-diisopropylphenol	0.1-5.0	1.0-2.0	1.0
Soybean Oil	1.0-30.0	10.0-30.0	10.0
Egg Phosphatide	0.2-2.0	0.7-2.0	1.2
Benzyl alcohol	0.0175-0.9	0.07-0.45	0.15
Sodium benzoate	0-0.07	0.07	0.07
Glycerol	2.0-3.0	2.35-2.75	2.25
Sodium Hydroxide	q.s.	q.s.	q.s.
Water for Injection	to 100	to 100	to 100

The compositions of the present invention may be used as is conventional in the art, e.g., for the induction of anesthesia prior to maintenance with a conventional inhalation anesthetic; as a sole anesthetic agent for short duration, by repeated administration, or by continuous infusion. The compositions of the invention may be used as a sole anesthetic agent of longer duration.

The invention is illustrated by the following representative examples:

10 Example 1

The compositions of the present invention may be formulated following procedures well known to those skilled in the art. Specific reference is made to U.S. Patent 5,714,520 which is hereby incorporated by reference.

15 Example 2

Propofol oil-in-water emulsions containing 0.45% benzyl alcohol/0.005% disodium EDTA, 0.035% benzyl alcohol/0.005% disodium EDTA, 0.45% benzyl alcohol/0.07% sodium benzoate, and 0.035% benzyl alcohol/0.07% sodium benzoate were tested by the USP 23 preservative effectiveness test as described in United States Pharmacopoeia 23-NF 18, 1995 Ed., Chapter 51, which is incorporated herein by reference. Briefly, this involves inoculating the test solution with 10^5 to 10^6 test organisms per milliliter and then determining the number of surviving organisms after 7, 14, 21, and 28 days incubation at 20-25 °C using standard microbiological methods. Day 0 data is not required by USP 23 but was included in this study. A filtration and buffer wash method was used to remove the inactivating agents for purposes of recovering the microorganisms, but other equivalent methods can also be validated for use. The USP test organisms include the bacteria *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*, a yeast (*Candida albicans*), and a mold (*Aspergillus niger*). In order to meet the criteria of the USP 23 preservative effectiveness test, the bacteria must demonstrate a 90% (1 logarithmic) reduction at Day 7 and a 99.9% reduction (3 logarithmic) reduction at Day 14 from the initial inoculum level. The initial inoculum level can either be calculated

knowing the stock culture concentration or by using a buffer control instead of the test solution. The results, using formulations which are 10% fat emulsions, are given below in Tables 2 through 5 where the number reported is the number of organisms per milliliter. ND means not detected, i.e., below the levels of detection by the assay. Although same 5 formulations did not meet the criteria of the USP test, in most cases they met the definition of "antimicrobial".

TABLE 2 (0.45% Benzyl Alcohol/0.005% Disodium EDTA)

10	Organism Time	<u>A. niger</u>	<u>C. albicans</u>	<u>E. coli</u>	<u>P. aeruginosa</u>	<u>S. aureus</u>
	Inoculum per ml product	390,000	440,000	750,000	460,000	610,000
15	0 Hr.	300,000	360,000	380,000	310,000	380,000
	Day 7	210,000	340,000	680	3,000	47,000
	Day 14	210,000	350,000	190	200	7,200
	Day 21	3,400	270,000	40	60	4,300
20	Day 28	130	105,000	10	10	1,020

TABLE 3 (0.035% Benzyl Alcohol/0.005% Disodium EDTA)

25	Organism Time	<u>A. niger</u>	<u>C. albicans</u>	<u>E. coli</u>	<u>P. aeruginosa</u>	<u>S. aureus</u>
	Inoculum per ml product	390,000	440,000	750,000	460,000	610,000
30	0 Hr.	300,000	310,000	360,000	310,000	430,000
	Day 7	300,000	330,000	40	105,000	36,000
	Day 14	210,000	310,000	<10 ND	68,000	3,500
	Day 21	120,000	320,000	<10 ND	67,000	740
35	Day 28	29,000	110,000	>10 ND	38,000	170

TABLE 4 (0.45 Benzyl Alcohol/0.07 Sodium Benzoate)

Organism Time	<u>A. niger</u>	<u>C. albicans</u>	<u>E. coli</u>	<u>P. aeruginosa</u>	<u>S. aureus</u>
Inoculum per ml product	390,000	440,000	750,000	460,000	610,000
0 Hr.	290,000	340,000	380,000	440,000	390,000
Day 7	260,000	390,000	86,000	101,000	30,000
Day 14	29,000	350,000	62,000	14,900	1,350
Day 21	22,000	203,000	80,000	2,800	100
Day 28	290	87,000	76,000	150	10

TABLE 5 (0.035Benzyl Alcohol/0.07%Sodium Benzoate)

Organism Time	<u>A. niger</u>	<u>C. albicans</u>	<u>E. coli</u>	<u>P. aeruginosa</u>	<u>S. aureus</u>
Inoculum per ml product	390,000	440,000	750,000	460,000	610,000
0 Hr.	370,000	450,000	420,000	550,000	520,000
Day 7	250,000	530,000	8,800,000	3,500,000	310,000
Day 14	130,000	410,000	7,100,000	3,400,000	92,000
Day 21	41,000	440,000	5,800,000	30,000	49,000
Day 28	13,000	300,000	2,180,000	7,000	22,100

Example 3

The antimicrobial properties of various propofol formulations were determined by a spiked hold time study. Briefly, a propofol formulation is inoculated to achieve approximately 100 organisms per 10 mL sample. The organisms used include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida albicans*, *Bacillus subtilis*, *Aspergillus niger*, and *Clostridium sporogenes*. The inoculated samples are held for various times and then filtered in duplicate. The filters are washed with buffer and then placed on appropriate agar growth media.

The antimicrobial agents should reduce the growth rate such that there is less than a 1 logarithm increase within a 24 hour period.

C. albicans presented the most resistance to the preservative system. The *C. albicans* results from the spiked hold time study are shown in Table 6 for various propofol formulations. *E. coli*, *P. aeruginosa*, and *B. subtilis* also demonstrated some resistance to the antimicrobial agents (data not shown).

The remaining test organisms increased less than 2-fold over the 7 day test period. The results are shown in organisms per mL of test solution. A value of >300 indicates too numerous to count; these data points may still meet the acceptance criteria of less than 1 logarithmic increase. In the Tables, BA = Benzyl Alcohol, NB = Sodium Benzoate. The percent of benzyl alcohol is indicated in w/v for each formulation. The percent Sodium benzoate, when present, is 0.07% (w/v).

TABLE 6

Formulation	0 hours	24 hours	48 hours	7 days
0.45 BA/NB	37	35	28	56
0.15 BA only	59	102	>300	>300
0.15 BA/NB	59	45	>300	>300
0.13 BA/NB	66	57	>300	>300
0.10 BA/NB	53	59	>300	>300
0.07 BA/NB	34	120	>300	>300
0.035 BA/NB	33	125	>300	>300
0.0175 BA/NB	38	185	>300	>300

Example 4

Propofol oil-in-water emulsions containing 0.45% benzyl alcohol/0.07% sodium benzoate, 0.035% benzyl alcohol/0.07% sodium benzoate, 0.035% benzyl alcohol/0.005% disodium EDTA, and 0.045% benzyl alcohol/0.005% disodium EDTA were tested by the USP 23 preservative effectiveness test as described in Example 2. The results, using formulations which are 1% fat emulsions, are given below in Tables 7 through 10 where the number reported in the number of organisms per milliliter. Lowering the percent oil, increased the effectiveness of the preservative(s) compound in Example 2.

TABLE 7 (0.45% Benzyl Alcohol/0.07% Sodium Benzoate)

Organism Time	<u>A. niger</u>	<u>C. albicans</u>	<u>E. coli</u>	<u>P. aeruginosa</u>	<u>S. aureus</u>
Inoculum per ml product	390,000	440,000	750,000	460,000	610,000
0 Hr.	470,000	1,000	<10 ND	1,200	<100
Day 7	33,000	<100	<10	<10	<100
Day 14	<10 ND	<100 ND	<10 ND	<10 ND	<100 ND
Day 21	<10 ND	<100 ND	<10 ND	<10 ND	<100 ND
Day 28	<10 ND	<100 ND	>10 ND	<10 ND	<100 ND

TABLE 8 (0.035% Benzyl Alcohol/0.07% Sodium Benzoate)

Organism Time	<u><i>A. niger</i></u>	<u><i>C. albicans</i></u>	<u><i>E. coli</i></u>	<u><i>P. aeruginosa</i></u>	<u><i>S. aureus</i></u>
5 Inoculum per ml product	390,000	440,000	750,000	460,000	610,000
0 Hr.	420,000	1,050	<10 ND	5,500	20
Day 7	200,000	<10 ND	<10 ND	5,200	<10 ND
Day 14	14,000	<10 ND	<10 ND	3,700	<10 ND
10 Day 21	14,000	<10 ND	<10 ND	4,100	<10 ND
Day 28	17,000	<10 ND	>10 ND	5,000	<10 ND

15

TABLE 9 (0.035% Benzyl Alcohol/0.005% Disodium EDTA)

Organism Time	<u><i>A. niger</i></u>	<u><i>C. albicans</i></u>	<u><i>E. coli</i></u>	<u><i>P. aeruginosa</i></u>	<u><i>S. aureus</i></u>
20 Inoculum per ml product	390,000	440,000	750,000	460,000	610,000
0 Hr.	460,000	112,000	<10 ND	680	100
Day 7	290,000	<10 ND	<10 ND	<10 ND	<100 ND
Day 14	4,100	<10 ND	<10 ND	<10 ND	<100 ND
25 Day 21	2,900	<10 ND	<10 ND	<10 ND	<100 ND
Day 28	2,700	<10 ND	>10 ND	<10 ND	<100 ND

TABLE 10 (0.45%Benzyl Alcohol/0.005% Disodium EDTA)

5	Organism Time	<i>A. niger</i>	<i>C. albicans</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>
	Inoculum per ml product	390,000	440,000	750,000	460,000	610,000
	0 Hr.	320,000	300	<10 ND	<10 ND	<10 ND
10	Day 7	260	<10 ND	<10 ND	<10 ND	<10 ND
	Day 14	<10 ND	<10 ND	<10 ND	<10 ND	<10 ND
	Day 21	<10 ND	<10 ND	<10 ND	<10 ND	<10 ND
15	Day 28	<10 ND	<10 ND	<10 ND	<10 ND	<10 ND

Example 5

Propofol oil-in-water emulsions containing 0.45%/benzyl alcohol/0.005%
 20 disodium EDTA and 0.45% benzyl alcohol/0.07% sodium benzoate were tested by the
 USP 23 preservative effectiveness test as described in Example 2. The results, using
 formulations which are 1% fat emulsions of a medium chain triglyceride oil, are given
 below in Tables 11 and 12 where the number reported is the number of organisms per
 milliliter.

25

TABLE 11 (0.45% Benzyl Alcohol/0.005% Disodium EDTA)

Organism Time	<u><i>A. niger</i></u>	<u><i>C. albicans</i></u>	<u><i>E. coli</i></u>	<u><i>P. aeruginosa</i></u>	<u><i>S. aureus</i></u>
Inoculum per ml product	390,000	440,000	750,000	460,000	610,000
0 Hr.	490,000	180	<10 ND	<10 ND	<10 ND
Day 7	28,000	<10 ND	<10 ND	<10 ND	<10 ND
Day 14	<10 ND	<10 ND	<10 ND	<10 ND	<10 ND
Day 21	<10 ND	<10 ND	<10 ND	<10 ND	<10 ND
Day 28	<10 ND	<10 ND	<10 ND	<10 ND	<10 ND

TABLE 12 (0.45% Benzyl Alcohol/0.07% Sodium Benzoate)

Organism Time	<u><i>A. niger</i></u>	<u><i>C. albicans</i></u>	<u><i>E. coli</i></u>	<u><i>P. aeruginosa</i></u>	<u><i>S. aureus</i></u>
Inoculum per ml product	390,000	440,000	750,000	460,000	610,000
0 Hr.	420,000	260	<10 ND	1,780	<10 ND
Day 7	20,000	<10 ND	<10 ND	<10 ND	<10 ND
Day 14	<10 ND	<10 ND	<10 ND	<10 ND	<10 ND
Day 21	<10 ND	<10 ND	<10 ND	<10 ND	<10 ND
Day 28	<10 ND	<10 ND	<10 ND	<10 ND	<10 ND

Claims

1. A sterile pharmaceutical composition comprising a propofol containing oil-in-water emulsion having as an antimicrobial agent, a member selected from the group
5 consisting of:
benzyl alcohol and sodium ethylene diamine tetraacetate;
benzethonium chloride; and
benzyl alcohol and sodium benzoate.
- 10 2. A composition according to claim 1 where the propofol is emulsified by means of a surfactant.
3. A composition according to claim 1 where the surfactant is an ethoxylated ether or ester, a polypropylene polyethylene block copolymer or a phosphatide.
15
4. A composition according to claim 1 where the surfactant is egg phosphatide.
5. A composition according to claim 1 where the propofol is dissolved in a water-immiscible solvent.
20
6. A composition according to claim 5 where the solvent is soy bean oil, safflower oil, cottonseed oil, corn oil, sunflower oil, arachis oil, castor oil or olive oil.
7. A sterile oil-in-water emulsion pharmaceutical composition comprising:
25 from 0.1 to 5.0 weight percent propofol;
from 2.0 to 30 weight percent solvent;
from 0.2 to 2.0 weight percent surfactant;
2.0 to 3.0% weight percent glycerol;
from 0.0175 to 0.9 weight percent of an antimicrobial agent selected from the
30 group consisting of:
benzyl alcohol and sodium ethylene diamine tetraacetate,
benzethonium chloride, and,

benzyl alcohol and sodium benzoate,
and the balance of the composition being water.

8. A method inducing anesthesia comprising administration of an effective
5 amount of the composition of claim 1.

9. The method of Claim 7 wherein the anesthesia is induced prior to
treatment with an inhalation anesthetic.

10 10. The method of claim 8 wherein the composition is the sole anesthetic
agent.

11. A method of inducing anesthesia comprising administration of an
effective amount of the composition of claim 7.
15

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/24347

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K9/107 A61K31/05 A61K47/10 A61K47/12 A61K47/18 A61P23/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 714 520 A (JONES CHRISTOPHER BUCHAN ET AL) 3 February 1998 (1998-02-03) cited in the application column 4, line 10 - line 45 column 5, line 1 - line 53 claims; examples	1-11
A	WO 97 10814 A (VESIFACT AG ;WEDER HANS G (CH)) 27 March 1997 (1997-03-27) page 3, line 9 - line 18 claims; example 1	1-11
<input type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents :		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"Z" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">24 February 2000</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">02/03/2000</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">Epskamp, S</div>

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 24347

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 8-11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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